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(54) Title: SUPERIORITY OF FORMULATIONS CONTAINING COENZYME Q_{10} IN COCONUT OIL

(57) Abstract

The present invention comprises a stable and non-toxic coenzyme Q_{10} formulation with superior bioavailability suitable for oral administration to an animal or a human to rapidly produce clinically effective blood levels of coenzyme Q_{10}. Clinically effective blood levels of coenzyme Q_{10} are generally agreed to be between about 2 μg/mL and about 4 μg/mL. The formulation consists of saturated vegetable oil, hydrogenated vegetable oil or animal fat as a vehicle in which coenzyme Q_{10} is dissolved. The formulation preferably contains coenzyme Q_{10} at a level of about 100 mg to about 150 mg dissolved in about 350 μL to about 500 μL of saturated vegetable oil, hydrogenated vegetable oil or animal fat enclosed in a gelatin capsule. The clinically accepted vegetable oil is saturated, preferably coconut oil.

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DESCRIPTION

SUPERIORITY OF FORMULATIONS CONTAINING COENZYME Q_{10} IN COCONUT OIL

BACKGROUND OF THE INVENTION

This invention relates to new formulations comprising coenzyme Q_{10} (CoQ_{10}) in saturated vegetable oils for use in clinical medicine. The saturated vegetable oils are those commonly used in the food and pharmaceutical industries.

Based on pharmacokinetic data from animals and healthy human subjects orally administered with currently available formulations of CoQ_{10} (2,3-dimethoxy-5-methyl-6-decaprenyl benzoquinone) dissolved in unsaturated vegetable oils, there is very slow absorption of CoQ_{10} as monitored, for example, by blood levels. In animals and in humans, oral supplementation with currently available formulations of CoQ_{10} in unsaturated vegetable oils is slow to produce clinically beneficial blood levels of CoQ_{10}, taking a minimum of 5-7 days in rats and 7-14 days in humans. This slow absorption may relate to the insolubility of CoQ_{10} in aqueous media and relatively low solubility of CoQ_{10} in unsaturated vegetable oils. Careful examination of the contents of capsules containing typical levels of about 33 mg of CoQ_{10} in 350 μL of unsaturated vegetable oil shows that as much as 50% of the CoQ_{10} has come out of solution. This undissolved CoQ_{10} will enter the aqueous milieu of the digestive tract, making its absorption unlikely. The extreme lipophilicity of CoQ_{10} also may explain why as much as 62% of an orally administered dose in unsaturated vegetable oil has been recovered from feces during a study period of 10 days. If feces were analyzed over a longer period, an even higher level of excretion of unchanged CoQ_{10} would be expected. The overall absorption of orally administered CoQ_{10} in unsaturated vegetable oil is expected to be in the range of 10-20% (Lucket *et al.*, 1984).

Since the mid-1960' s, investigators have demonstrated the benefits of supplementation with CoQ_{10} on the symptoms of cardiomyopathy in human patients and in increase of blood

CoQ_{10} levels to about 2 μg/mL (Langsjoen, *et al.*, 1994). Elevations of blood levels of CoQ_{10} from normal (about 0.7 μg/mL) or even lower, as is common in these patients, to clinically desirable levels typically requires supplementation at a level of about 100 mg/day to about 600 mg/day. Supplementation at these levels can require the patient to swallow up to eighteen or more capsules per day. Cardiomyopathy patients are clinically characterized into four classes according to a system developed by the New York Heart Association (NYHA). Those patients in NYHA Class IV are in very serious condition and are near death. While oral supplementation has been associated with clinical and functional improvements in all NYHA Classes of patients, the most critical need is for improvement, especially rapid improvement, of the Class IV patient. For many of these patients a few days can differentiate between survival and death. Severe Class IV patients must be aggressively treated if they are to survive.

Coenzyme Q_{10}, being highly hydrophobic, is essentially insoluble in aqueous solutions. For CoQ_{10} to be absorbed in the digestive tract, it must be contained in a stable formulation in which it will remain dispersed under conditions of normal storage and use. Currently available oral supplements include CoQ_{10} in a tablet or capsule form mixed with one or more dry inert ingredients or CoQ_{10} partially dispersed in unsaturated vegetable oil in a gelcap. Some formulations of each type also include other biologically active substances, *e.g.*, vitamin E. Since oral supplements are administered with water or some other aqueous solution, the formulations which are tablets or dry powder capsules are associated with very slow absorption. Those formulations based on dispersal of CoQ_{10} in unsaturated vegetable oil (usually soybean oil) either have very low CoQ_{10} content, *e.g.*, 10 mg/capsule, or have higher CoQ_{10} concentrations, *e.g.*, 33 mg/capsule, in which 30-50% of the CoQ_{10} has separated from the oil. The prominent problem in developing a highly bioavailable oil-dispersed formulation relates to the fact that CoQ_{10} is solid at temperatures below 50°C. Unsaturated vegetable oils can be warmed to levels at or above 50°C to allow dispersal of about 33 mg of CoQ_{10} per 350 μL of oil (the oil content of a standard gelcap), but cooling of the mixture to room temperature results in a significant amount of the CoQ_{10} falling to the bottom of the container. Gently warming the unsaturated oil/CoQ_{10} to body temperature does not fully re-disperse the separated CoQ_{10}. It is likely that the undispersed CoQ_{10}, like that in the tablets and dry capsules, is poorly absorbed.

Another approach has been to use formulations of unsaturated vegetable oils containing CoQ_{10} and a dispersant. While this does result in a product in which the CoQ_{10} remains dispersed at room temperature, animal studies have shown no significant improvement in blood levels over those formulations without the dispersant. To date, available formulations, though effective over time, have not been shown to produce a rapid rise to clinically effective, sustained blood levels.

SUMMARY OF THE INVENTION

The present invention comprises a stable and non-toxic CoQ_{10} formulation with superior bioavailability suitable for oral administration to an animal or a human to rapidly produce clinically effective blood levels of CoQ_{10}. Clinically effective blood levels of CoQ_{10} are generally agreed to be between about 2 μg/mL and about 4 μg/mL. The formulation consists of saturated vegetable oil as a vehicle in which CoQ_{10} is dissolved. The formulation preferably contains CoQ_{10} at a level of about 100 mg to about 150 mg dissolved in about 350 μL to about 500 μL of saturated vegetable oil enclosed in a gelatin capsule. The clinically effective vegetable oil is saturated, preferably coconut oil.

The present invention also comprises a method for preparing a stable and non-toxic CoQ_{10} formulation with superior bioavailability suitable for oral administration to an animal or a human to produce clinically effective blood levels of CoQ_{10}. This method involves the mixing of CoQ_{10} with a saturated vegetable oil which has been warmed to 50°C to achieve a formulation having a CoQ_{10} concentration of about 100 mg per 350 μl of oil. The CoQ_{10} is most preferably added to coconut oil and mixed by any of the many well-known means, such as the use of a magnetic stirrer on an electric warming plate.

The present method also includes a method for raising blood levels of CoQ_{10} to a clinically effective level in an animal or a human. The method comprises first obtaining a stable and non-toxic CoQ_{10} formulation with superior bioavailability, preferably comprising a mixture of CoQ_{10} in a saturated vegetable oil such as coconut oil, such that the concentration of CoQ_{10} in the mixture is about 100 mg per 350 μL of oil. The next step is to encapsulate the

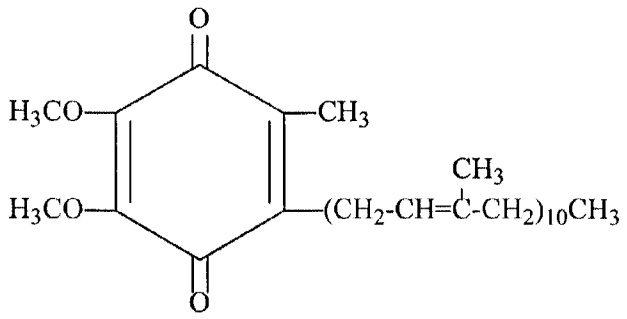
mixture such that the resultant capsule will contain about 100 mg of CoQ_{10}. The capsule can then be administered orally to an animal or a human to achieve a blood level of CoQ_{10} of between about 2 μg/mL and about 4 μg/mL.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the results of a bioavailability study comparing a formulation of coenzyme Q_{10} in soybean oil to one in coconut oil.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Coenzyme Q_{10} is essentially insoluble in aqueous media. This insolubility is related to the 50-carbon atom isoprenoid side chain, of hydrocarbon nature, as shown in the following structure of CoQ_{10}.



Data from animal and human studies have shown that intestinal absorption of commonly available formulations is slow and inefficient. It often takes from one to several weeks of supplementation to achieve clinically effective blood levels of CoQ_{10}. This slow absorption is likely related to the aqueous insolubility of CoQ_{10} because of its extreme lipophilicity. Currently available CoQ_{10} formulations are either dry tablets or capsules containing CoQ_{10} in solid form mixed with a dry inert substance; are low concentrations of CoQ_{10} mixed in unsaturated vegetable oil requiring many capsules to be taken; or are higher

concentrations of CoQ_{10} in unsaturated vegetable oil in which much of the CoQ_{10} has separated from the oil. These formulations provide all or significant amounts of the CoQ_{10} to the intestinal tract in solid form, which will not dissolve in the aqueous milieu of the intestinal tract. As disclosed herein, a formulation has been devised of CoQ_{10} thoroughly dispersed in saturated vegetable oil (coconut oil) in which oral administration may provide increased bioavailability as evidenced by a rapid attainment of a clinically effective blood concentration of CoQ_{10}.

The more bioavailable oral CoQ_{10} formulations of the present invention allow for rapid delivery of clinically effective amounts of CoQ_{10} into blood for transport to organs such as liver and heart and other tissues for therapeutic benefit. In contrast, the slowly absorbed formulations in current use may be ineffective for acute and life-threatening clinical situations due to their poor bioavailability. A rapid and efficient absorption into blood is essential for patients who need maximum benefit of the potentially life-saving and/or life-extending activities of CoQ_{10}.

A clinically effective and usable oral formulation of CoQ_{10} should be stable at common ambient temperatures and remain essentially unchanged in dispersion characteristics for a period of at least a year, because this period would be about that required for preparation; analysis; shipment to distribution centers; shipment to and storage in hospitals, offices and homes until use, etc.

The object of the present invention is the achievement of a formulation of CoQ_{10} in saturated vegetable oil which has excellent dispersion, stability and bioavailability characteristics. As disclosed herein, such a formulation has been produced and is safe and effective for medical use. One embodiment of the present invention is a formulation consisting essentially of a dispersion of CoQ_{10} in coconut oil which has excellent dispersion, stability and bioavailability characteristics.

Toward achieving a superior formulation, the present inventors prepared and tested a variety of formulations against the commonly available formulation of about 33 mg of CoQ_{10} in about 350 μL of soybean oil, which is the best of the currently available formulations. In

clinical medicine, patients are typically given 100 mg to 600 mg of such a CoQ_{10} formulation per day, thus requiring that from about three to about 18 capsules be taken. At the concentration level of 33 mg of CoQ_{10} in 350 μL of soybean oil, a significant portion of the CoQ_{10} typically separates as solid CoQ_{10} during storage at room temperature. Gentle warming to 37°C, body temperature, as would occur when a capsule is swallowed, does not result in a complete redispersal of the CoQ_{10}. Therefore, less than the full dose of such preparations is dispersed in the absorbable oil milieu.

In an effort to develop a formulation with improved bioavailability, the present inventors undertook a series of experiments using CoQ_{10} in soybean oil as the comparison standard. Initially, a number of commonly available unsaturated vegetable oils were compared to soybean oil as the basis for improved bioavailability. Safflower oil, peanut oil, olive oil and corn oil were compared to soybean oil. An identical amount of CoQ_{10} was dispersed into equal volumes of each oil. On standing at room temperature, separation of CoQ_{10} from the dispersion was seen in all oils. In repeated trials, identical amounts of each mixture were administered to animals via gavage. Small but clinically unimportant differences in blood and liver CoQ_{10} levels were found. Therefore, in this study, no important advantage was gained by any unsaturated oil formulation over the soybean oil standard.

Next, the use of emulsifiers or dispersants in unsaturated vegetable oil formulations was tried. The use of emulsifiers is common in the food and pharmaceutics industries as a means of improving the dispersal of lipophilic substances in aqueous milieus. As in the initial trials of unsaturated vegetable oils discussed hereinabove, CoQ_{10} in soybean oil was used as the reference standard. In repeated trials, identical amounts of formulations with unsaturated vegetable oils containing the same concentrations of CoQ_{10} and also including an emulsifier such as lecithin, bile salts, or Nikkol™ (a commercially available dispersant from Nikkol Chemicals Co., Ltd.) were administered to animals via gavage. As in the initial trials with unsaturated vegetable oils, none of the formulations of CoQ_{10} in unsaturated vegetable oils with emulsifiers were shown to give important improvements in blood and liver concentrations of CoQ_{10} as compared to CoQ_{10} in soybean oil.

Next, an aqueous formulation was prepared in which the CoQ_{10} was first dispersed in warmed Nikkol™ which was then dissolved in water. This formulation was compared to CoQ_{10} in soybean oil at identical concentration by administering each formulation to animals via gavage. Again, no important differences in blood or liver concentrations of CoQ_{10} were seen.

Thus, a new series of trials was begun using a saturated vegetable oil, coconut oil, in which CoQ_{10} was dispersed. As before, CoQ_{10} dispersed in soybean oil was used as the reference standard. In this experiment, the levels of CoQ_{10} in the liver of rats increased to significant levels within one day using the coconut oil formulation while the soybean oil formulation took five days to achieve a similar level. A trial in a human subject showed that a significant increase in blood CoQ_{10} levels from 1.6 μg/mL to 2.6 μg/mL was seen in only three days on the coconut oil formulation as compared to no change (1.6 μg/mL to 1.6 μg/mL) in three days on the soybean formulation. Ten days were required for this human subject to achieve the same blood level with the soybean oil formulation as was achieved in three days with the coconut oil. The combination of data from the above animal and human experiments suggests that the coconut oil preparation gives superior bioavailability of coenzyme Q_{10} relative to other currently available formulations.

In another experiment both soybean oil and coconut oil formulations were significantly ($p<0.005$) better than a placebo but were not significantly different from each other. The results of this study are shown in **FIG. 1**. As **FIG. 1** shows, (i) both formulations produced a significant increase in blood levels of subjects supplemented at the level of 100 mg/day as compared to a placebo; (ii) in this experiment the two formulations were not significantly different from each other at any point in the project; and (iii) both formulations achieved a blood level plateau within 7 days of supplementation. This result suggests that the primary advantage of the new formulation is simply that one capsule of 100 mg of coenzyme Q_{10} in a coconut oil formulation is equivalent to three capsules of 33.3 mg of coenzyme Q_{10} in a soybean oil formulation. However, this is of no small consequence for patients who have been taking 18 or more of the soybean oil capsules per day. In fact, one capsule of the coconut oil

formulation can be made to contain as much as 150 mg of CoQ_{10}, giving a clear advantage over existing oil formulations.

Coenzyme Q_{10} dispersed at the level of 100 mg in 350 μL of coconut oil has a melting point of about 33°C, which is below human body temperature (37°C). Coenzyme Q_{10} is completely dispersed in coconut oil at this concentration at room temperature and remains so at lower temperatures to which the formulation might expect to be exposed, *e.g.*, during refrigeration. Pure triglycerides were tested as possible dispersants. Concentrations of 100 mg of CoQ_{10} in 350 μL of trilaurin and of tristearin were found to have melting points well above body temperature (45°C and 71°C, respectively), making them unsuitable for formulations contemplated for human use. Here, the coconut oil formulation proved superior to formulations comprising pure triglycerides.

Any patient in severe, Class IV cardiomyopathy is in imminent threat of death. Increasing blood concentrations of CoQ_{10} to a level between about 2.0 μg/mL and about 4.0 μg/mL has been shown to be clinically beneficial. The more rapidly a clinically beneficial blood level can be achieved, the lower the risk of death in the patient. The formulation described in this invention may achieve a desirable rapid increase in blood levels of CoQ_{10} not achievable with certain existing formulations.

The examples listed herein illustrate the design and preparation of superior oral formulations of CoQ_{10} for use in clinical medicine. The saturated vegetable oil present in our exemplary formulation is coconut oil. The use of other saturated vegetable oils such as hydrogenated unsaturated oils (*e.g.*, corn, soy, peanut, olive, canola, cottonseed, safflower, rice, wheat, *etc.*) or such as palm or other tropical oils, or such as saturated fats from animal sources, are within the scope of this invention. The fact that some of these oils naturally contain CoQ_9 or CoQ_{10} in trace amounts does not exclude their use in the preparation of saturated oil formulations because the level of CoQ_9 or CoQ_{10} is a trace which would have little metabolic significance.

The saturated fat formulations of the present invention may be used, for example, to provide 100 mg to 150 mg of CoQ_{10} in 350 μL of coconut oil per capsule. Advantageously,

this increased level of CoQ_{10} per capsule above the currently available 33 mg of CoQ_{10} in 350 μL of soybean oil allows the use of fewer capsules to achieve a comparable or higher blood level in a patient. Thus, one capsule of 100 mg of CoQ_{10} in coconut oil may be superior to three capsules of 33 mg of CoQ_{10} in soybean oil.

Coenzyme Q_{10}-coconut oil formulations have been prepared for oral administration to patients. These formulations will allow for the development of a clinically effective blood level of between about 2.0 μg/mL and about 4.0 μg/mL within a relatively short time period. It is common in clinical medicine to administer up to 600 mg CoQ_{10} per day (*i.e.* eighteen 33 mg capsules) in an attempt to achieve a blood level of between about 2.0 μg/mL and about 4.0 μg/mL and this may require several weeks. The current formulation not only achieves a clinically effective blood level quickly, but may do so at lower daily dosages than with current formulations.

The preferred technique for preparing a formulation of the present invention involved the addition of CoQ_{10} to warm (50°C) coconut oil at a level of 100 mg of CoQ_{10} in 350 μL of coconut oil. After the CoQ_{10} was completely dispersed in the oil, the mixture was then cooled to room temperature to form an orange (due to the color of CoQ_{10}) solid having the consistency of vegetable shortening. This was sufficient for the purposes of the laboratory preparation as appropriate (*e.g.* 350 μL) doses could be measured out and used. In commercial preparations, the mixture is preferably encapsulated into soft gel capsules.

At the concentrations of 100 mg to 150 mg of CoQ_{10} in 350 μL of coconut oil, the CoQ_{10} did not separate at room temperature, under refrigeration, nor upon chilling to 0°C. Whereas, the soy oil preparation at a concentration of 33 mg in 350 μL of soybean oil noticeably separated at room temperature, and especially under refrigeration, and even more so at 0°C. When a small aliquot of the solid mixture of CoQ_{10} and coconut oil was applied to the skin of the back of the hand it very quickly melted into a uniform orange colored liquid which quickly spread over and into the skin. When a small drop of the liquid mixture of the soybean oil formulation containing separated CoQ_{10} was placed on the skin of the back of the hand, the oil quickly spread across the skin but, even after several minutes, small pieces of CoQ_{10} remained intact as separate bits of solid. This suggests that any improved uptake into the blood

may be due to the complete and stable dispersal of CoQ_{10} in the coconut oil and the ease with which the CoQ_{10} remains in lipid solution at body temperature.

It is known that CoQ_{10} is stable in the currently available soft gelatin capsules in which it is dispersed with soybean oil for up to six years. Since saturated oils are more chemically stable than unsaturated oils (*e.g.*, soybean oil), it is anticipated that the formulation of CoQ_{10} in coconut oil will be as stable or more stable than the soybean oil formulations. The stability of the formulations described in this invention will be sufficient to meet all commercial and medical needs for stability.

Since CoQ_{10} has a clinical record of safety over two decades and a record of stability of over 6 years in soybean oil capsules, and since coconut oil is widely and safely used within the food and pharmaceutical industries, the CoQ_{10}-coconut oil formulation of the present invention provides assurance of safety and stability and efficacy of therapeutic benefit, particularly, for example, in cardiology.

The above described preparation procedure was on a laboratory scale and may be appropriately modified and scaled up to allow the production of unlimited amounts of the CoQ_{10}-coconut oil formulation for commercial use. The appropriate changes in procedure between the laboratory and factory scale production are readily determined and are within the scope of this invention.

The exemplary formulations of the present invention will allow the use of a minimal number of capsules to achieve a medically important blood level of CoQ_{10} of about 2.0 μg to about 4.0 μg/mL. Advantageously, this blood level may be achieved more quickly than with current formulations, and this may prove critically important for end-stage cardiomyopathy patients.

To appreciate the importance and utility of the saturated vegetable oil CoQ_{10} formulations of the present invention, it is helpful to reiterate the limitations and negative aspects of currently available unsaturated oil formulations. In both animal models and in human patients, pretreatment with CoQ_{10} has been shown to reduce the injury to the myocardium due to ischemia and reperfusion damage which may occur during heart surgery. A

formulation such as that of the present invention may allow for pretreatment of the patient for a day or two to achieve a blood level which may help to decrease the myocardial injury due to ischemia and perfusion seen in procedures such as coronary by-pass surgery. Survival rate for this type of surgical procedure should be improved with pretreatment with this formulation. Patients with Class IV cardiomyopathy, who have severe disease and are in a life-threatening situation, are only questionably benefited by pretreatment with currently available CoQ_{10} formulations because of the slow and erratic absorption of unsaturated oil-CoQ_{10} formulations. It is conceivable that patients with Class IV cardiomyopathy may benefit from the rapidly absorbed coconut oil-CoQ_{10} formulation of this invention, whereas they may not benefit from a few days of pretreatment with certain other currently available dry or unsaturated oil formulations.

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CLAIMS

Changes may be made in the construction, operation and arrangement of the various elements, steps and procedures described herein without departing from the concept and scope of the invention as defined in the following claims.

1. A stable and non-toxic coenzyme Q_{10} formulation suitable for oral administration to an animal or human to produce clinically effective blood levels of coenzyme Q_{10}, the formulation consisting essentially of a clinically accepted mixture comprising a lipid phase and coenzyme Q_{10} dissolved in the lipid phase at a level of between about 100 mg and about 150 mg per 350 μl.

2. The formulation of claim 1, wherein the lipid phase is a saturated vegetable oil or a saturated animal fat.

3. The formulation of claim 1, wherein the lipid phase is a vegetable oil.

4. The formulation of claim 1, wherein the lipid phase is coconut oil.

5. The formulation of claim 3, wherein the vegetable oil is at least one of coconut oil, palm oil, hydrogenated corn oil, hydrogenated soybean oil, hydrogenated peanut oil, hydrogenated safflower oil, hydrogenated cottonseed oil, hydrogenated olive oil, hydrogenated wheat oil, or hydrogenated rice oil.

6. The formulation of claim 2, wherein the saturated animal fat is beef lard or pork lard.

7. The formulation of claim 1, wherein the clinically effective blood levels of coenzyme Q_{10} are between about 2.0 μg/mL and about 4.0 μg/mL.

8. The formulation of claim 1, wherein the formulation is defined further as being essentially free of exogenous detergent.

9. A method for preparing a stable and non-toxic coenzyme Q_{10} formulation suitable for oral administration to an animal or human to produce clinically effective blood levels of coenzyme Q_{10}, the method comprising thoroughly mixing a clinically accepted lipid with an amount of coenzyme Q_{10} sufficient to result in a formulation having a coenzyme Q_{10} concentration between about 100 mg and about 150 mg per 350 μl of lipid.

10. The method of claim 9, wherein the lipid is at least one saturated vegetable oil, hydrogenated vegetable oil or animal fat.

11. The method of claim 9, wherein the lipid is coconut oil.

12. The method of claim 10, wherein the saturated vegetable oil is at least one of coconut oil, palm oil and other tropical oil; the hydrogenated vegetable oil is at least one of corn oil, soybean oil, safflower oil, canola oil, peanut oil, cottonseed oil, rice oil, wheat oil and olive oil; the animal fat is at least one of beef lard and pork lard.

13. The method of claim 9, further defined to include mixing the coenzyme Q_{10} with the lipid with mild warming.

14. The method of claim 9, wherein the clinically effective blood levels of coenzyme Q_{10} are between about 2.0 μg/mL and about 4.0 μg/mL.

15. The method of claim 9, wherein the formulation is defined further as being essentially free of exogenous detergent.

16. A method for raising blood levels of coenzyme Q_{10} to clinically effective levels in an animal or human, the method comprising:

obtaining a stable and non-toxic formulation comprising a clinically accepted lipid and coenzyme Q_{10} at a concentration between about 100 mg and about 150 mg per 350 μl of lipid

orally administering said formulation to the animal or human to achieve blood levels of coenzyme Q_{10} of between about 2.0 μg/mL and about 4.0 μg/mL.

17. The method of claim 16 wherein the lipid is at least one saturated vegetable oil, hydrogenated vegetable oil or animal fat.

18. The method of claim 17 wherein the saturated vegetable oil is at least one of coconut oil, palm oil and other tropical oil; the hydrogenated vegetable oil is at least one of corn oil, soybean oil, safflower oil, canola oil, peanut oil cottonseed oil, rice oil, wheat oil and olive oil; the animal fat is at least one of beef lard and pork lard.

19. The method of claim 16 wherein the formulation is defined further as being essentially free of exogenous detergent.

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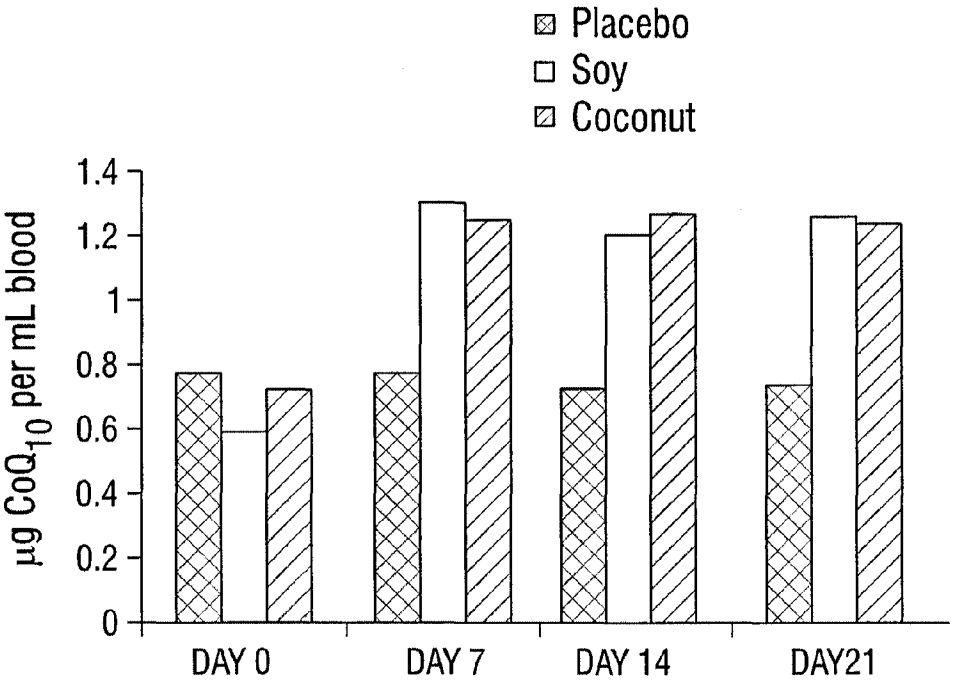
Placebo
Soy
Coconut
μg CoQ10 per mL blood
1.4
1.2
1
0.8
0.6
0.4
0.2
0
DAY 0
DAY 7
DAY 14
DAY21

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11827

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/175
US CL :514/689, 690

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/689, 690

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPATFULL, WPIDS, HCAPLUS, BIOSIS, REGISTRY, FSTA, BIOTECHDS, DRUGU, JAPIP, JICST-EPI, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,011,858 A (LANGSJOEN et al) 30 April 1991, see entire document.	1-3, 5 --- 4, 1-19
X -- Y	US 5,180,747 A (MATSUDA et al) 19 January 1993, see entire document.	1-3, 5 --- 4, 6-19
X -- Y	US 4,869,900 A (POZZI et al) 26 September 1989, see entire document.	1-3, 5 --- 4, 6-19
X -- Y	Database HCAPLUS on STN, Chemical abstracts, (Columbus, Ohio, USA), Accession No. 1982: 28598, JP 57042616 A2 (FUROINTO SANGYO K.K.), 1982, "Ubiquinones with improved bioavailability." 10 March 1982.	2-3, 5, 7-8, 16-19 --- 4, 6, 9-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 JULY 1998	02SEP1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Rebecca Cook Telephone No. (703) 308-1235

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